Remarks/Arguments

Amendments to the Claims

This amendment cancels claims 1-12, 22-23, 26-27, 29-32 that are not elected or traversed by Applicants. Applicants reserve the right to pursue the non-elected subject matter in a subsequent divisional application(s).

Claim 20, directed to polynucleotides of the TNFRSF1A isogenes is amended to delete Applicants' reference TNFRSF1A isogene, isogene 22. In addition, since the substitute sequence listing enclosed herein includes a sequence for each of the TNFRSF1A isogenes, Claim 20 has been amended to refer to Sequence Id Numbers. Support for this amendment is found in claim 20 as originally filed and in the specification at p. 39, lines 5-7 and in Table 5 (pp. 39-40).

Claim 25 is amended to claim each of the four coding sequences claimed in the originally filed claim 25.

Claim 28, directed to a polymorphic fragment of a TNFRSF1A coding sequence, is amended to require a length of at least 15 nucleotides and to include the nonreference allele at each of the four polymorphic sites found within the coding sequence. Support for this amendment to claim 28 is found in Figure 2, claim 25 as originally filed and in the specification at p.26, lines 32-34.

Claim 34, drawn to genome anthologies, is amended to direct the claim to collections of two or more TNFRSF1A isogenes encoding a TNFRSF1A polypeptide with a domain capable of binding TNFα. This amendment more clearly focuses this claim on collections of isogenes included within the scope of the polynucleotides of claim 20. Additionally, claim 34 has been amended to refer to Sequence Id Numbers for each of the 27 isogenes. Support for this amendment can be found in the claim as originally filed and in the specification at p.2, lines 42-34; p. 39, lines 5-7; and in Table 5 (pp. 39-40).

Amendments to the Sequence Listing

The Substitute Sequence Listing submitted herewith includes a sequence for each TNFRSF1A isogene disclosed in the specification. Support for the additional sequences in the Substitute Sequence Listing is found in SEQ ID NO:1 of the Sequence Listing as originally submitted, in claim 20 as originally filed, and in the specification at p. 39, lines 5-7; and in Table 5 (pp. 39-40). For convenience, the table below provides the information correlating TNFRSF1A isogene number with SEQ ID NO. in the Substitute Sequence Listing.

TNFRSF1A isogene no.	SEQ ID NO.
1	42
2	43
3	44
4	45
5	46
6	47
7	48
8	49
9	50
10	51
11	52
12	53
13	54
14	55
15	56
16	57
17	58
18	59
19	60
20	61
21	62
22	63
23	64
24	65
25	66
26	67
27	68

Restriction/Election

The Office Action required restriction between the following groups:

I Claims 1-8;

II: Claims 9-10;

III. Claims 11-12;

IV. Claims 13-21, 24-25, 28, 35-39;

V. Claims 22-23, 26-27;

VI. Claims 29, 32;

VII Claim 30;

VIII. Claim 31; and

IX. Claim 34.

Applicants hereby elect Group IV, with traverse with respect to restriction between Group IV (Claims 13-21, 24-25, 28, 35-39), and Group IX (Claim 34). The Office Action also asserts that Group IV and Group IX contain independent and distinct inventions, and further requires election of a single invention within Group IV, or election of two inventions within Group IX.

With respect to the additional restriction requirement within Group IV, Applicants hereby elect, with traverse, invention 2, which corresponds to specific TNFRSF1A isogene and coding sequences defined by haplotype 2 in Table 5 on p. 39 of the specification. Invention 2 also corresponds to SEQ ID NO: 43 in the Substitute Sequence Listing submitted herewith. The Office Action, and subsequent telephone communications with the E,xaminer, indicated that if Group IV were elected, then Applicants should provide oligonucleotides that are specific for the elected TNFRSF1A isogene and coding sequence. Below is a table including sequence id numbers and/or nucleotide positions in SEQ ID NO:43 for allele-specific probes and primers for genotyping each of the polymorphic sites 1-18 (PS1-PS18) for the alleles present in isogene 2 (SEQ ID NO:43).

	ASO Probes[1]	
PS No.	SEQ ID NO.	nucleotide positions in SEQ ID NO:43
1	4, wherein K=G	
2		3401-3417
3		3430-3446
4	5, wherein S=C	
5		4046-4062
6		4074-4090
7		11990-12006
8		12348-12364
9		12389-12405
10		12481-12497
11		12645-12661
12	6, wherein R = G	
13		14982-14998
14	7, wherein Y=C	
15	8, wherein Y=C	
16		15521-15537
17	9, wherein R = G	
18	10, wherein R = G	

[1]Note that complements of each of the sequences in the above table of ASO probes for a given PS No. is also a functional ASO probe for detecting the allele at that PS NO. in the selected isogene.

	ASO Primers			
PS No.	SEQ ID NO.	SEQ ID NO.	nucleotide positions in SEQ ID NO:43	complement of nuc. positions in SEQ ID NO:43
1	11, wherein K=G	12, wherein M= C		
2			3396-3410	3408-3422
3			3425-3439	3437-3451
4	13, wherein S=C	14, wherein S = G		
5			4041-4055	4053-4067
6			4069-4083	4081-4095
7			11985-11999	11997-12011
8			12343-12357	12355-12369

	ASO Primers			
PS No.	SEQ ID NO.	SEQ ID NO.	nucleotide positions in SEQ ID NO:43	complement of nuc. positions in SEQ ID NO:43
9			12384-12398	12396-12411
10			12476-12490	12488-12502
11			12640-12654	12652-12666
12	15, wherein R = G	16, wherein Y=C		
13			14977-14991	14989-15003
14	17, wherein Y=C	18, wherein R = G		
15	19, wherein Y=C	20, wherein R = G		
16			15516-15530	15528-15542
17	21, wherein R = G	22,wherein Y=C		
18	23, wherein R = G	24,wherein Y=C		

In the event that the Patent Office withdraws the requirement for restriction between Group IV and Group IX, Applicants hereby elect with traverse, inventions 2 and 12, which correspond to TNFRSF1A isogenes defined by haplotypes 2 and 12 in Table 5 on p. 39 of the specification or SEQ ID NOS: 43 and 53, respectively.

Traversal of the Restriction Between Group IV and Group IX

Applicants respectfully request that Group IX (claim 34), which is directed to a genome anthology of TNFRSF1A isogenes, be rejoined with elected Group IV (claims 3-21, 24-25, 28, 35-39), which is directed to polynucleotides comprising TNFRSF1A isogene and coding sequences, fragments of these polynucleotides, and to oligonucleotides for genotyping certain polymorphic sites within the TNFRSF1A gene.

The Office Action states that the inventions in Groups IV and IX are distinct. Restriction between distinct inventions is only proper when one of the following is shown by appropriate explanation: (A) separate classification thereof; (B) a separate status in the art when they are classifiable together; or (C) a different field of search. See MPEP §808.02. Applicants respectfully assert that the Office Action has not provided an appropriate explanation for any of these criteria.

With respect to the separate classification criterion, Applicants respectfully assert that the Office Action has misclassified claim 34 in Class 707, subclass 1. Class 707, according to the Manual of Patent Classification, is a generic class for data processing apparatus and corresponding methods for the retrieval of data stored in a database or as computer files. Subclass 1 is described as pertaining to subject matter directed to the retrieval of data stored in a database or as computer files, where a file is defined as a named collection of data. However, claim 34 is directed to a genome anthology of two or more of the TNFRSF1A isogenes discovered by Applicants. Genome anthologies are defined in the specification as collections of at least two TNFRSF1A isogenes (see p. 25, lines 11-22), which are nucleic acids, not a data processing apparatus. Since the claims in Group IV are also directed to nucleic acids, including TNFRSF1A isogenes, claim 34

should have the same classification as the claims in Group IV.

In addition to being classifiable together, Applicants respectfully assert that restriction can not be properly maintained under the second criterion set forth in MPEP §808.02 because the inventions within Group IV and claim 34 do not have a separate status in the art. For a restriction requirement to rely on reason (B), the requirement must provide an appropriate explanation that even "though they are classified together, each subject can be shown to have formed a separate subject for inventive effort". (MPEP §808.02) The claims of Group IV are directed to nucleic acids, including TNFRSF1A isogenes. Claim 34 is also directed to nucleic acids, specifically to collections of at least two of the TNFRSF1A isogenes within the scope of the claims of Group IV. Determination of the sequences of the TNFRSF1A isogenes and the other nucleic acids of Group IV was achieved by a single inventive effort by the Applicants. Since the genome anthologies of Claim 34 are merely collections of two or more of the TNFRSF1A isogenes within the scope of Group IV, the genome anthologies of Claim 34 were determined by the very same inventive effort resulting in the claims of Group IV. Consequently, the claims of Group IV, drawn to TNFRSF1A nucleic acids, and claim 34, drawn to collections of TNFRSF1A nucleic acids, do not have separate status in the art and may not properly be restricted based on reason (B).

Finally, with respect to the third criterion set forth in §808.02, the Office Action merely alleged that divergent literature and sequence searches for Group IV and Group IX would be required, but did not provide any explanation as to why divergent searches would be required. As demonstrated above, the reason for divergent searches can not depend on a separate classification, since claim 34 should be classified with Group IV.

Indeed, Applicants submit that a separate field of search should not be required to examine claim 34 and the claims in Group IV for novelty and nonobviousness. As noted above, claim 34 is directed to collections of at least two TNFRSF1A isogenes, which are nucleic acids, and the claims in Group IV are directed to TNFRSF1A nucleic acids, including TNFRSF1A isogenes. Since each of the TNFRSF1A nucleic acids in Claim 34 or Group IV involve the sequence of the same human gene, the same genomic backbone structure, and one or more of the same set of 18 polymorphic sites within the TNFRSF1A sequence, Applicants respectfully assert that the same sources of prior art (e.g., scientific literature on the TNFRSF1A gene, sequence databases, polymorphism databases, and the like) would need to be searched. Further supporting Applicants' assertion that the same sources of prior art would need to be searched for Group IV and claim 34 is the fact that elected isogene 2 for Group IV is identical to one of the two elected isogenes for claim 34, isogene 2 and 12. Applicants respectfully assert that the Patent Office may not maintain a restriction between the claims of Group IV and claim 34 based on different literature and sequence searches without stating *how* they would be different.

Traversal of the Restriction Between Inventions within the scope of Claim 20 of Group IV

The Office Action requires election of a single invention between the different inventions within Group IV (claims 13-21, 24-25, 28, 35-39), which appear to be defined by the Office Action as the 27 TNFRSF1A isogenes within the scope of claim 20. The Office Action emphasizes that this required election is not a species election. Applicants traverse this restriction requirement for the following reasons.

Claim 20 is directed to a genus of TNFRSF1A isogene sequences that encode a TNFRSF1A polypeptide with a domain capable of binding TNFα, and to the complements of these sequences. The different isogene sequences within the genus of claim 20 are defined by a Markush group of specified TNFRSF1A haplotypes. The restriction of independent claim 20 is contrary to well-established law and patent practice. A restriction requirement may not be applied to a single Markush claim. *In re Weber*, 198 USPQ 328 (CCPA 1978; *In re Haas (II)* 198 USPQ 334; MPEP 803.02. The only proper reason for the Patent Office to refuse to examine a Markush claim in its entirety is when the Patent Office finds that the subject matter in the claim lacks unity of invention. *In re Harnisch*, 206 USPQ 300 (CCPA 1980; MPEP 803.02). However, the Office Action did not allege that the TNFRSF1A isogene sequences specified by the Markush group lack unity of invention and thus failed to establish a prima facie case that restriction within claim 20 is proper.

Applicants respectfully assert that the Patent Office must examine the entire Markush group in claim 20 because the subject matter of the Markush group in claim 20 has unity of invention. Unity of invention in a Markush group exists when its members "(1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility." MPEP §803.02.

The first part of this test is met because all of the alternative TNFRSF1A isogenes within the scope of claim 20 share the *common utility* of encoding a TNFRSF1A polypeptide with a domain capable of binding TNFα. In fact, all but five of these claimed TNFRSF1A isogenes encode the exact same TNFRSF1A polypeptide (SEQ ID NO:3), (compare SEQ ID NO:1, SEQ ID NO:2 and the individual haplotypes represented in Table 5 on pp.39-40 of the specification) whose ability to bind TNFα is well-established in the art. The remaining five isogenes, isogenes 8, 9, 14, 17 and 19, each encode one of four TNFRSF1A polypeptides, each of which differs from SEQ ID NO:3 at only one residue. The single amino acid change in each of these four polypeptides has a Grantham ranking (R. Grantham, 1974 *Science* 185:862-4) as being a conservative or a moderately conservative substitution. Single conservative amino acid substitutions are present in the polypeptides encoded by isogene 8 (a substitution of glutamine for arginine at position 121 in SEQ ID NO:3) and isogene 19 (a substitution of lysine for arginine at position 312 in SEQ ID NO:3). The moderately conservative substitutions are present in the polypeptide encoded by isogenes 14 and 17 (a substitution of leucine for proline at position 75 in SEQ ID NO:3) and the polypeptide encoded by isogene 9 (a substitution of histidine for tyrosine at position 135 in SEQ ID NO:3). Applicants respectfully

assert that one skilled in the art would expect that TNFRSF1A polypeptides with these conservative and moderately conservative substitutions would still have a domain that is capable of binding TNFα. Thus, each member within the Markush group has a common utility as required by MPEP §803.02.

Additionally, as required by the second part of the test set forth in MPEP §803.02, the alternative isogenes of claim 20 share a significant structural element that is essential to their ability to encode a TNFRSF1A polypeptide with a domain capable of binding TNFα. Out of the roughly 4900 nucleotides of the sequenced regions of the genomic structure, the claimed TNFRSF1A isogenes differ from the previously known version of the TNFRSF1A gene by a maximum of only 18 bases and are therefore at least 99.6% identical to that version. Moreover, as is evident by examining the TNFRSF1A isogene and coding sequences specified by SEQ ID NO:1, SEQ ID NO:2 and Table 5 on pp.39-40 of the specification, the 27 isogene sequences enumerated in the Markush group differ from each other by at most only one base out of the 1368 nucleotides that make up the coding region of the TNFRSF1A gene, making each of the claimed TNFRSF1A isogenes at least *99.9%* structurally identical to the previously known TNFRSF1A isogene in the coding region, a region that would be considered by the skilled artisan to be structurally significant for an isogene that is to encode a polypeptide with a domain that is capable of binding TNFα. Thus, Applicants assert that the high level of structural identity of the TNFRSF1A isogenes across the gene, and the even higher level of structural identity in the coding region, constitutes the significant structural element shared by each of these isogenes that is essential to their common utility of encoding a polypeptide with a domain that is capable of binding TNFα. Thus, the restriction within independent claim 20 is contrary to well-established law and patent practice and must be withdrawn.

Traversal of the Restriction Between Inventions within Claim 34

The Office Action requires election of two inventions between the different inventions within Group IX (claim 34), and emphasizes that this required election is not a species election. Applicants traverse this restriction requirement for the following reasons.

The Office Action states that Group IX (claim 34) is drawn to 27 independent and distinct inventions corresponding to the 27 haplotypes disclosed in Table 5 in the specification. The Office Action states that these inventions are independent and distinct because "a molecule of haplotype 1, comprising a particular combination of polymorphisms, differs chemically, structurally, and functionally from a molecule of haplotype 2".

Group IX (claim 34) is directed to a genus of genome anthologies, or collections of isogenes. Independent inventions, according to MPEP §802.01, "are unconnected in design, operation, or effect". The TNFRSF1A genome anthologies within the scope of claim 34 are not unconnected in design, operation or effect, and are therefore not independent. Each genome anthology comprises two or more of the 27 TNFRSF1A isogenes disclosed in the instant application. The 27 TNFRSF1A isogenes, as noted above, are

at least 99.6% identical structurally, differing by a maximum of only 18 bases out of the roughly 4900 nucleotides of the sequenced regions of the genomic structure, with an even higher level of structural identity in the coding region, i.e., the region of the isogene which constitutes the significant structural element shared by each of these isogenes that is essential to their common utility, established above, of encoding a TNFRSF1A polypeptide with a domain that is capable of binding TNFα. Since the 27 TNFRSF1A isogenes are therefore related structurally and functionally, they are not independent inventions but are instead related, distinct inventions. Further, since the individual TNFRSF1A isogenes comprising each genome anthology are related distinct inventions, the various species of genome anthologies within the scope of claim 34 are not independent, but are related distinct inventions.

MPEP 806.04 states that "[w]here inventions as disclosed and claimed are both (A) species under a claimed genus and (B) related, then the question of restriction must be determined by both the practice applicable to election of species and the practice applicable to other types of restrictions such as those covered in MPEP §806.05- §806.05(i). If restriction is improper under *either* practice, it should not be required." (emphasis added).

Restriction between distinct inventions is only proper when one of the following is shown by appropriate explanation: (A) separate classification thereof; (B) a separate status in the art when they are classifiable together; or (C) a different field of search. See MPEP §808.02. Applicants respectfully assert that the Office Action has not provided an appropriate explanation for any of these criteria.

The Office Action has classified all the inventions within the scope of claim 34 within the same class: Class 707, subclass 1. Applicants' have argued above that the subject matter of claim 34, genome anthologies, which are collections of TNFRSF1A nucleic acids, are better classified with the similar subject matter of the claims in Group IV, also directed to nucleic acids. Each species of genome anthology within the scope of claim 34 is composed of two or more TNFRSF1A isogenes selected from the isogenes disclosed in the instant application. Consequently, the species within the scope of claim 34 can not be classified in separate classes because they do not have recognition in the art as separate subjects nor do they require separate fields of search since each species is a collection of TNFRSF1A nucleic acids. Restriction of Claim 34 can not be properly maintained under the first criterion.

In addition to being classifiable together, Applicants respectfully assert that restriction can not be properly maintained under the second criterion set forth in MPEP §808.02 because the inventions within the scope of claim 34 do not have a separate status in the art. For a restriction requirement to rely on reason (B), the requirement must provide an appropriate explanation that even "though they are classified together, each subject can be shown to have formed a separate subject for inventive effort". (MPEP §808.02) Claim 34 is directed to TNFRSF1A genome anthologies, collections of at least two of the TNFRSF1A isogenes disclosed in the application. Determination of the sequences of the 27 TNFRSF1A isogenes, and therefore the possible collections of these isogenes within the scope of claim 34 was achieved by a single inventive effort by the

Applicants. Consequently, the genome anthologies within the scope of claim 34do not have separate status in the art and may not properly be restricted based on reason (B).

Finally, with respect to the third criterion set forth in §808.02, as demonstrated above, the reason for divergent searches can not depend on a separate classification, since the species within the scope of claim 34 should be classified in the same class. Applicants submit that a separate field of search should not be required to examine the different species of genome anthologies of claim 34 for novelty and nonobviousness. As noted above, claim 34 is directed to collections of at least two TNFRSF1A isogenes. Since each of the TNFRSF1A genome anthologies in Claim 34 involve two or more isogene sequences of the same human gene, each with the same genomic backbone structure, and the same set of 18 polymorphic sites within the TNFRSF1A sequence, Applicants respectfully assert that the same sources of prior art (e.g., scientific literature on the TNFRSF1A gene, sequence databases, polymorphism databases, and the like) would need to be searched. Applicants respectfully assert that the Patent Office may not maintain a restriction between the genome anthologies within the scope of claim 34 based on different literature and sequence searches without stating *how* they would be different.

Thus, the restriction of independent claim 34 is improper under the restriction practice applicable to distinct inventions and therefore restriction between the species of claim 34 is improper under MPEP §806.04(b).

For the foregoing reasons, Applicants believe that reconsideration of the restriction requirement is warranted. Applicant's undersigned agent will be contacting the Examiner to request a phone interview with the Examiner and her supervisor to discuss Applicants' reasons for traversal.

Respectfully submitted,

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